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Journal Title: JAAD Case Reports
Volume: Volume 4, Number 7
Publisher: Elsevier | 2018-08-01, Pages 672-674
Type of Work: Article | Final Publisher PDF
Publisher DOI: 10.1016/j.jdcr.2018.03.021
Permanent URL: https://pid.emory.edu/ark:/25593/tbgqv

Final published version: http://dx.doi.org/10.1016/j.jdcr.2018.03.021

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Accessed October 3, 2019 1:25 PM EDT
Cutaneous thrombotic vasculopathy related to poorly controlled ulcerative colitis

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Cutaneous gangrene caused by thrombotic vasculopathy is a rarely described extraintestinal complication of ulcerative colitis.1-5 We report a case of cutaneous thrombotic vasculopathy associated with poorly controlled ulcerative colitis, possibly caused by enteric losses of antithrombin III.

CASE REPORT
A 33-year-old white woman presented to the hospital with a 1-day history of a rapidly progressing, painful, racemose purpuric eruption involving her chest, shoulders, arms, back, buttocks, and thighs. Smaller purpuric macules and patches had also formed on the bilateral ears, neck, and dorsal surfaces of her feet (Figs 1 and 2).

She was discharged from the hospital 3 days earlier after being admitted for evaluation of a 4-month history of bloody diarrhea. Colonoscopy during that hospital admission revealed superficial mucosal ulceration with a loss of a vascular pattern, extending 35 cm to the sigmoid colon from the anal verge. Colorectal biopsy specimens revealed findings consistent with chronic active colitis and proctitis. A diagnosis of ulcerative colitis was made. She was started on high-dose methylprednisolone and discharged on prednisone 60 mg/day. However, after discharge, she continued to have 8 to 9 episodes of bloody diarrhea per day, sometimes passing blood clots.

Serologic studies obtained during the present hospitalization revealed a leukocytosis with left shift (18.6 x 10^3/mcL; normal range, 4.0-10.0 x 10^3/mcL), hemoglobin 13.4 gm/dL (normal range, 11.4-14.4 gm/dL), and normal platelet count (163 x 10^3/mcL; normal range, 150-400 x 10^3/mcL). Coagulation studies showed a prolonged prothrombin time of 18.2 seconds (normal range, 9.4-12.5 seconds), normal partial thromboplastin time of 30.5 seconds (normal range, 25.1-36.5 seconds), an international normalized ratio of 1.57, fibrinogen level of 345 mg/dL (normal range, 200-393 mg/dL), low antithrombin III activity assay of 80% (normal range, 83-128%), and elevated d-dimer of 51,523 mg/mL (normal range, <574 mg/mL).

The silica clotting time and dilute Russell viper venom time screen ratios were within the normal reference range. Enzyme-linked immunosorbent assay for anticardiolipin, anti-β2-glycoprotein 1, antiphosphatidylerine immunoglobulin M and immunoglobulin G, and antiprothrombin immunoglobulin G antibodies were all normal.

Additional tests for activated protein C resistance, factor V Leiden, prothrombin gene mutation, and paroxysmal nocturnal hemoglobinuria were negative or normal. Antinuclear antibodies and extractable nuclear antigen antibodies, complement components 3 and 4, rheumatoid factor, and cryoglobulins were all negative or normal. A urine drug screen for cocaine was also negative.

Skin biopsy specimens of her back showed thrombotic vasculopathy but no vasculitis (Fig 3).

Computed tomography scans of the chest, abdomen, and pelvis with and without intravenous contrast did not demonstrate any evidence of thromboembolism. Venous Doppler ultrasonography of the bilateral lower extremities was normal. A magnetic resonance imaging scan of the brain showed no evidence of ischemic or embolic phenomena. Transesophageal echocardiography showed normal biventricular function and did not reveal endocardial clot or masses.
The patient was diagnosed with cutaneous thrombotic vasculopathy related to poorly controlled ulcerative colitis. She was treated with a high-intensity heparin drip with rapid improvement in cutaneous pain, followed by recession of the existing racemose purpuric patches and macules (Fig 4). However, while receiving high-intensity heparin, the patient required antithrombin boluses to achieve goal anti-Xa levels and therapeutic antithrombin III activity. Although on anticoagulation, the patient did not experience worsening hematochezia.

Infliximab infusions were administered with eventual diminution in stool frequency. The patient was transitioned from a heparin drip to subcutaneous enoxaparin 1.5 mg/kg/day. She was discharged after 13 days of hospitalization, still receiving enoxaparin and was instructed to continue infliximab infusions on an outpatient basis. She was later transitioned from enoxaparin to a direct oral anticoagulant and continued to do well, without recrudescence of tender, cutaneous purpura.

**DISCUSSION**

Cutaneous gangrene resulting from thrombotic vasculopathy is a rare and poorly understood extraintestinal manifestation of inflammatory bowel disease, most commonly ulcerative colitis. Hypercoagulable states and thromboembolism are more common in patients with inflammatory bowel disease compared to control subjects, possibly because of thrombocytosis, abnormal platelet
function, endothelial dysfunction, elevation of serum procoagulants (ie, fibrinogen, factor V, factor VII, and von Willebrand factor), and depletion of anticoagulants (ie, antithrombin, protein C, and protein S).\textsuperscript{6,7} Depletion of antithrombin may be linked to losses through a damaged enteric barrier, because elevated antithrombin levels have been detected in the stool of patients with ulcerative colitis and acquired antithrombin deficiency.\textsuperscript{8} Losses of antithrombin and resultant thrombosis has also been described in other forms of protein-losing enteropathies.\textsuperscript{9,10}

Selective loss and or depletion of antithrombin seems especially applicable to our case, given the exclusion of other prothrombotic etiologies and consistently low anti-Xa and antithrombin III levels while receiving a high-intensity heparin drip.

Cutaneous thrombotic vasculopathy is a rare but morbid extraintestinal manifestation of ulcerative colitis. Thrombotic vasculopathy should be suspected in a patient with known or occult inflammatory bowel disease who presents with rapidly progressive racemose purpura. Depending on the personal and family history of the patient, workup for acquired and possibly inherited disorders of coagulation may be undertaken to better understand the pathomechanisms of thrombosis in these individuals. Despite enteric blood losses from perturbed mucosal integrity, anticoagulation should not be withheld to limit the extent and severity of cutaneous infarction. Additional measures aimed at controlling underlying inflammatory bowel disease are warranted.

We thank Laura DeLong Aspey, MD, Emily Gurnee, MD, Aliza Lipson, MD, and Brian Willis, MD.

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